A Unique Pattern of Sleep Structure is Found to be Identical at all Cortical Sites: a Neurobiological Interpretation

Helli Merica and Ronald D Fortune[1]

Laboratoire de Sommeil et de Neurophysiologie, Hôpitaux Universitaires de Genève, Belle Idée, 1225 Chêne-Bourg, Geneva, Switzerland and [1]CERN European Organisation for Nuclear Research, 1211 Geneva 23, Switzerland

There is substantial evidence both at the cellular and at the electroencephalogram (EEG) level to support the view that the brainstem activating systems control the sleep-state (stage) progression over time that constitutes the overall sleep structure as seen at the EEG. We argue here that the brainstem therefore modulates the time-courses of spectral power in the different EEG frequency bands. These show during non-rapid eye movement (NREM) sleep a very particular interrelationship the origin of which has received little attention and for which the neuronal transition probability model for sleep structure has proposed a physiological explanation. We advance the hypothesis that if the brainstem is modulating these time-courses then they should show a marked similarity in shape and timing at all sites. Using data from 10 healthy subjects, we measure the degree of similarity of the time-courses over each of the first four NREM episodes at the frontal, central and parietal sites, for each of the frequency bands beta, sigma and delta, and also the cortically generated slow oscillation. All the cross-correlation coefficients are high and statistically significant, indicating that the shape and timing of these time-courses are practically identical at different sites despite regional differences in their average power levels. These results tend to suggest that two processes may operate concurrently: the brainstem controls the shape and timing of the power time-courses while cortical–thalamic interaction controls their site-dependent average power.

Introduction

Over the past decade considerable advances have been made in identifying the key nuclei and neuronal circuitry involved in the control of sleep [for reviews see (Steriade and McCarley, 1990; Pace-Schott and Hobson, 2002; Saper *et al.*, 2001)]. An increasingly clear picture emerges of the permanent dialogue between cortical and sub-cortical structures that gives rise to the characteristic electrical activity of the brain typifying the different sleep states or stages as identified at the electro-encephalogram (EEG). These basic findings clearly involve global changes in brain activity, where the hypothalamus, brainstem, thalamus and cortex have major interacting roles. The sleep state (stage) progression over time that constitutes the overall sleep structure as seen at the EEG has been investigated both at the cellular and at the EEG levels.

Cellular neurophysiology provides evidence that the reciprocal interaction between the sleep promoting neurons in the ventrolateral preoptic (VLPO) region of the hypothalamus and the arousal systems in the upper brainstem controls the sleep–wake states (Gallopin *et al.*, 2000; Saper *et al.*, 2001). Moreover, Szymusiak *et al.* (Szymusiak *et al.*, 1998) showed that the VLPO sleep promoting neurons increase their firing rate at sleep onset and that the firing rate increases proportionally with sleep depth. This progressive increase is mirrored at the brainstem neurons by a progressive decrease in their firing rate. As a result of the diminished brainstem excitatory input to the thalamus, thalamocortical neurons gradually become more hyperpolarized, leading first to light sleep (spindle oscillatory mode) then at a more hyperpolarized level to deep slow wave sleep (clock-like delta mode). Conversely, increased brainstem excitatory input depolarizes the thalamocortical cells, producing a transition to wake or rapid eye movement (REM) sleep (Steriade and McCarley, 1990). There thus exists a direct parallelism between brainstem firing-rate change and the move at the EEG from fast to spindle rhythm (Steriade, 1984), and from non-rapid eye movement (NREM) sleep to wake or REM sleep (Steriade *et al.*, 1997). The cellular basis underlying the generation of the various EEG rhythms (spindles, delta waves and the slow oscillation) characterizing the NREM sleep stages has also been studied intensely. The sites of origin and the basic mechanisms that underlie each of these rhythms have largely been elucidated (Steriade *et al.*, 1993a,b,c; Amzica and Steriade, 1997; Contreras *et al.*, 1997; McCormick and Ball, 1997). It has been shown that these do not appear at the EEG as 'pure' rhythms, but due to the integrating networks comprising cortical, reticular thalamic and thalamocortical neurons, several rhythms are grouped together into complex wave sequences. The cortex and thalamus thus form a 'unified oscillatory machine' in which the depolarizing component of the cortically generated slow oscillation has a major role in triggering, shaping and synchronizing thalamically generated rhythms as well as fast oscillations (Steriade and Amzica, 1998; Steriade, 2001). The intensity of this slow cortical oscillation is under brainstem control since it is initiated by the progressive deafferentation of the forebrain following decreased firing rate in the brainstem activating systems, and disappears when either the brainstem–thalamic–cortical system or the cortically projecting basal forebrain system is activated (Steriade *et al.*, 1993d). Taken together, the above findings support the view that the brainstem activating system exercises direct control of the sleep-state progression within NREM sleep, each state being defined by the EEG.

Although for more than half a century, the hypnogram has provided a rather subjective means to visualize this stage-wise progression of sleep, more quantitative information on the continuous nature of sleep structure can be drawn from sequential spectral analysis. This technique, which circumvents the second-by-second detail of individual waveforms, has proved itself over many years to be an important tool in the study of the EEG. It provides a means by which the complex wave sequences can be analysed by their frequency components, and concentrates essentially on longer term spectral power time-course (SPTC) phenomena. Using this approach, both human and animal data show that at the thalamus and at the cortex there exists a characteristic and well-defined relationship between the SPTCs for the major frequency bands beta sigma and delta (Lancel *et al.*, 1992; Aeschbach and Borbély, 1993; Uchida *et al.*, 1994a,b; Merica and Blois, 1997; Merica and Fortune, 1997). This relationship is summarized in Figure 1, where each sleep

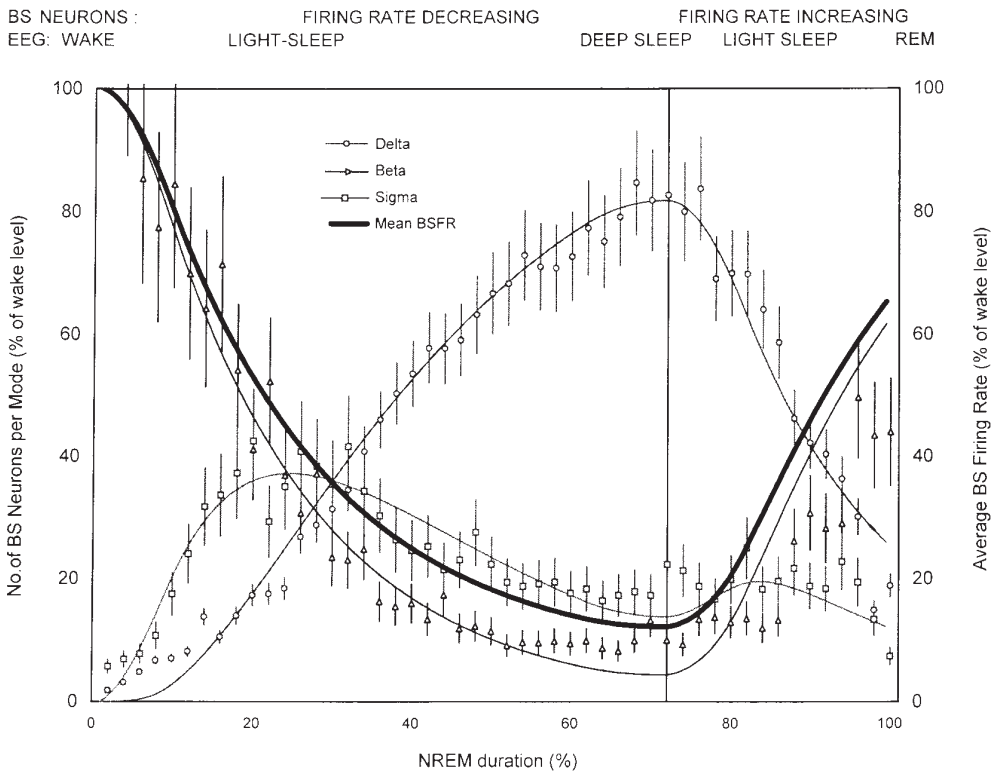

Figure 1. NREM 1 spectral power time-course data averaged over several subjects for the frequency bands beta, sigma and delta, fitted by the NTP model, and an estimate for the corresponding shape of the brainstem (BS) firing rate evolution. According to the NTP model, the weighted average of these time-courses should give the shape of the average brainstem firing rate (BSFR) time-course — as shown in heavy solid line. This average at any given time t is calculated by weighting each proportion p_i at that time by the corresponding brainstem firing-rate f_i, giving $F(t) = \Sigma(f_{it}\, p_{it})$. We have taken the rates to be in the ratio (14:2:1) for beta:sigma:delta, more or less in line with the literature, but the exact ratios are not important. This calculation gives the approximate shape of the average brainstem firing rate time-course as observed within the NREM episode: a quasi-exponential decrease followed by a rather sharper increase, reflecting the process of going towards deep sleep and then going away from it. Adapted from Merica and Fortune (Merica and Fortune, 1997).

state is seen to be associated with the preponderance of each of the time-course components. For brevity, we define the shapes, timing and relationships of the time-courses for the three bands as the 'pattern'. This pattern is a very fundamental characteristic of sleep structure that has received little attention *per se*. In our view, however, it is the very essence of minute-by-minute long-term sleep structure within the NREM episode.

It would thus be eminently reasonable to suppose that if the brainstem activating system is modulating sleep state progression, then it is *a fortiori* modulating the beta, sigma and delta power time-courses. It is in line with this reasoning that we hypothesized in our neuronal transition probability (NTP) model for sleep structure (Merica and Fortune, 2000) that the pattern originates in the slowing down followed by the speeding up of the firing rates of the neurons of the brainstem activating system (Fig. 1). Under this hypothesis the pattern is propagated intact to all downstream sites, with the consequence that however complex it may be, it should be reproduced in a similar manner at all cortical sites. This similarity has not so far been supported by direct topographical evidence, except for two preliminary studies: Bos *et al*. (Bos *et al*., 1977), measuring only the delta band, showed that the SPTCs measured at different topographical sites have 'extremely good similarities' suggesting to them the existence of a 'central modulator'. They did not, however, follow up this study, and were unable to deduce any underlying generating mechanism, because to do so, in our view, requires data on the beta and sigma bands as well. More recently, Ferrara *et al*. (Ferrara *et al*., 2002a), in a study covering only the first 30 min of sleep, reported regional similarities of the SPTCs for delta sigma and to a lesser extent for beta. In the present study, we search for evidence in support of our hypothesis on brainstem modulation of the SPTCs. This we do by examining over each of the first four NREM episodes the degree of similarity of the SPTCs at different topographical sites, for each of the frequency bands beta sigma and delta, and also for the cortically generated slow oscillation band.

Materials and Methods

Subjects

The study uses data from 10 healthy paid volunteers aged between 23 and 29 years (mean age 25.2 ± 2.4 years) from whom informed consent was obtained in accordance with Ethical Committee requirements. The data were selected randomly from our data bank of all-night sleep recordings carried out under controlled environmental conditions. All subjects were screened for good health on the basis of their history and clinical examination and asked to refrain from excessive caffeine and alcohol consumption on the days preceding nocturnal polysomnography.

EEG Recording, Data Extraction and Spectral Analysis

All-night sleep was recorded using three bipolar EEG derivations (F4-Cz, C4-T4 and Pz-O2), one horizontal electrooculogram, one submental electromyogram, an electrocardiogram and respiration (monitored by thermistors under the nostrils). Sleep stages were visually scored every 20 s using Rechtschaffen and Kales (Rechtschaffen and Kales, 1968) rules. The EEG signals were high-pass and low-pass filtered (0.5 and 70 Hz) and digitized at a sampling rate of 256 Hz with a 12-bit resolution. Prior to analyses, the signals were subjected to an automatic 1 s resolution artefact

detection routine using a background-dependent filter based on the root mean square amplitude of the signals. After visual validation, all epochs containing artefacts were coded as missing data so as to preserve time continuity. Then, for each EEG signal, power spectra in units of μV^2 were computed by fast Fourier transform with a Hanning window, for consecutive 4 s epochs over a frequency range 0.5–35 Hz. This range was divided into four frequency bands – slow oscillation (0.5–1 Hz), delta (1–4 Hz), sigma (12–15 Hz) and beta (15–35 Hz) – and power was moving-averaged with a window of 180 s. The delta band range includes two different oscillations: a thalamically generated clock-like delta (1–4 Hz), arising from the interplay of two intrinsic currents of thalamocortical neurons, and a cortically generated delta (3–4 Hz) that survives thalamectomy. However, it is believed that the latter 'takes place on a limited scale' and therefore should not mask clock-like delta activity (Amzica and Steriade, 1998). Sleep staging and signal analysis were done using the Era software package (PHITOOLS, Grenoble, France).

REM and NREM episodes were separated using the 15 min combining rule for defining the end of a REM episode (Feinberg and Floyd, 1979; Merica and Gaillard, 1991). No minimum duration of REM sleep was required in order to define the start of a REM episode. The start of the first NREM episode was set at sleep onset. The epoch that immediately followed the end of a REM episode gave the start for the following NREM episode. We retained the first four NREM episodes for study.

Statistical Analysis

Statistical analyses were carried out on each NREM episode using the time-courses of power in each frequency band. The time series data for each frequency band and subject at the three different sites were log-transformed and cross-correlation coefficients calculated between each pair of sites using all data pairs for the 10 subjects together. In this way we avoided the pitfalls of calculating correlation coefficients between time-courses averaged over all subjects. These analyses were done using the SYSTAT software package.

Results

Figure 2 shows for one typical subject of the 10 measured, the marked similarity between frontal, central and parietal sites, for the shapes of the SPTCs for the delta, sigma and beta frequency bands. This similarity – evident from a visual perusal – is underlined by a perfect coincidence in the time of occurrence of the major peaks and troughs in each band. As seen on the ordinate scale the results are independent of differences in average power at the different sites. For frontal, central and parietal sites respectively these averages are 468, 222, 220 (delta), 31, 20, 19 (sigma) and 6.3, 3.2, 3.3 (beta) in units of μV^2. Since cross-correlation coefficients ignore such differences they can be used as an objective measure of the similarities in shape. Table 1 gives these coefficients calculated for each frequency band, for each NREM episode and over all 10 subjects. Figure 3 shows for the same subject the marked similarity between frontal, central and parietal sites, for the shapes of the cortically generated slow oscillation SPTCs, with average power levels 207, 109 and 118 μV^2, respectively. Table 2 gives the cross-correlation coefficients for this band. All correlations are high and statistically significant, indicating that the time series from different topographical regions are time-locked with essentially zero phase lag.

The pattern characteristics that inspired the NTP model (Merica and Fortune, 1997; Merica and Fortune, 2000) can be seen in Figure 2 by comparing the delta, sigma and beta panels: the typical multiple delta peaks within each NREM episode, a characteristic of individual night data that is not seen on data averaged over several subjects; the clear and repeated precedence of a sigma peak before each delta peak; the initial exponential fall of beta and the almost mirror image relation between delta and beta. The time constant for the beta fall is ~7 min, which corresponds to the arrival of the sigma maximum. The time constant for the delta fall is ~2 min. This very particular relationship between the time-courses is present in all NREM episodes of all subjects and we have shown that the NTP model fits it well (Merica and Fortune, 2000).

Discussion

The results clearly show that in each of the first four NREM episodes, and for each of the four frequency bands studied, the time-courses at all sites are practically identical in respect to shape and timing, with any differences due mainly to random fluctuations. This agrees in general with preliminary results on similarity reported in the literature (Bos *et al.*, 1977; Ferrara *et al.*, 2002a). The suggestion by Ferrara *et al.*, however, that there may be significant regional differences for the beta time-courses, is in apparent contradiction with our results and deserves closer scrutiny. Their methodology may explain the discrepancy: instead of estimating the inter-site cross-correlation directly as we do, they compare beta–delta correlations at the different sites. Moreover, unlike us, they use averaged time-course data for their analyses. Averaging effectively conceals the structure of the individual time-courses constituting the average because of wide inter-individual variation in shape and timing (Merica and Fortune, 2000). Despite this their Figure 2 does not appear to substantiate their claim that the beta time-course at the frontal lead differs significantly from that at the other sites in the second half of the 30 min interval studied. A visual appraisal suggests to us that their beta time-courses are very similar at all sites and would undoubtedly give rise to a significant beta–beta correlation. There would thus appear to be no real disagreement. In addition to our main results, our data show that the average power level of the SPTCs differ between topographical sites, being highest in the frontal and lowest in the posterior regions. Although not a primary concern here, this is in line with a number of studies that have focused on the issue of regional differences in average spectral power (Jobert *et al.*, 1992; Kattler *et al.*, 1994; Werth *et al.*, 1996; Cajochen *et al.*, 1999; Vyazovskiy *et al.*, 2000; Achermann *et al.*, 2001; Anderer *et al.*, 2001; Finelli *et al.*, 2001; Ferrara *et al.*, 2002b; Knoblauch *et al.*, 2002). The question that arises is: what is (are) the brain structure(s) that could give rise to these two distinct types of observation, one on similarity of shape and timing of power time-courses and the other on differences in the average power of the time-courses?

The strong similarities we observe in SPTCs at different cortical sites suggest that, as proposed by Bos *et al.* (Bos *et al.*, 1977), there exists a central modulator governing them. Their reasoning, and ours, is the simple and natural response to the contemplation of any set of identical objects: they very probably have a common origin, a template from which they are copied, and most important, a template located outside of and distinct from any of the objects. Since the brainstem activating systems would appear to modulate the sleep states and hence all of the time-courses, including the slow oscillation, the brainstem is the most likely location of the template. This reasoning is the basis of our hypothesis that the population of wake-promoting neurons localized at several centres in the brainstem and diencephalon constitutes the central modulator in question. As outlined in the introduction, this hypothesis finds support in a large body of data: (i) there exists a clear parallelism between firing-rates at the brainstem and the EEG vigilance states. (ii) NREM episodes show a systematic precedence of the sigma peak before the delta peak, both at the cortex and at the thalamus. This characteristic precedence is explained at the single cell level by the voltage-dependency of sleep rhythms in thalamocortical cells, which are modulated by the firing rates of cholinergic and other

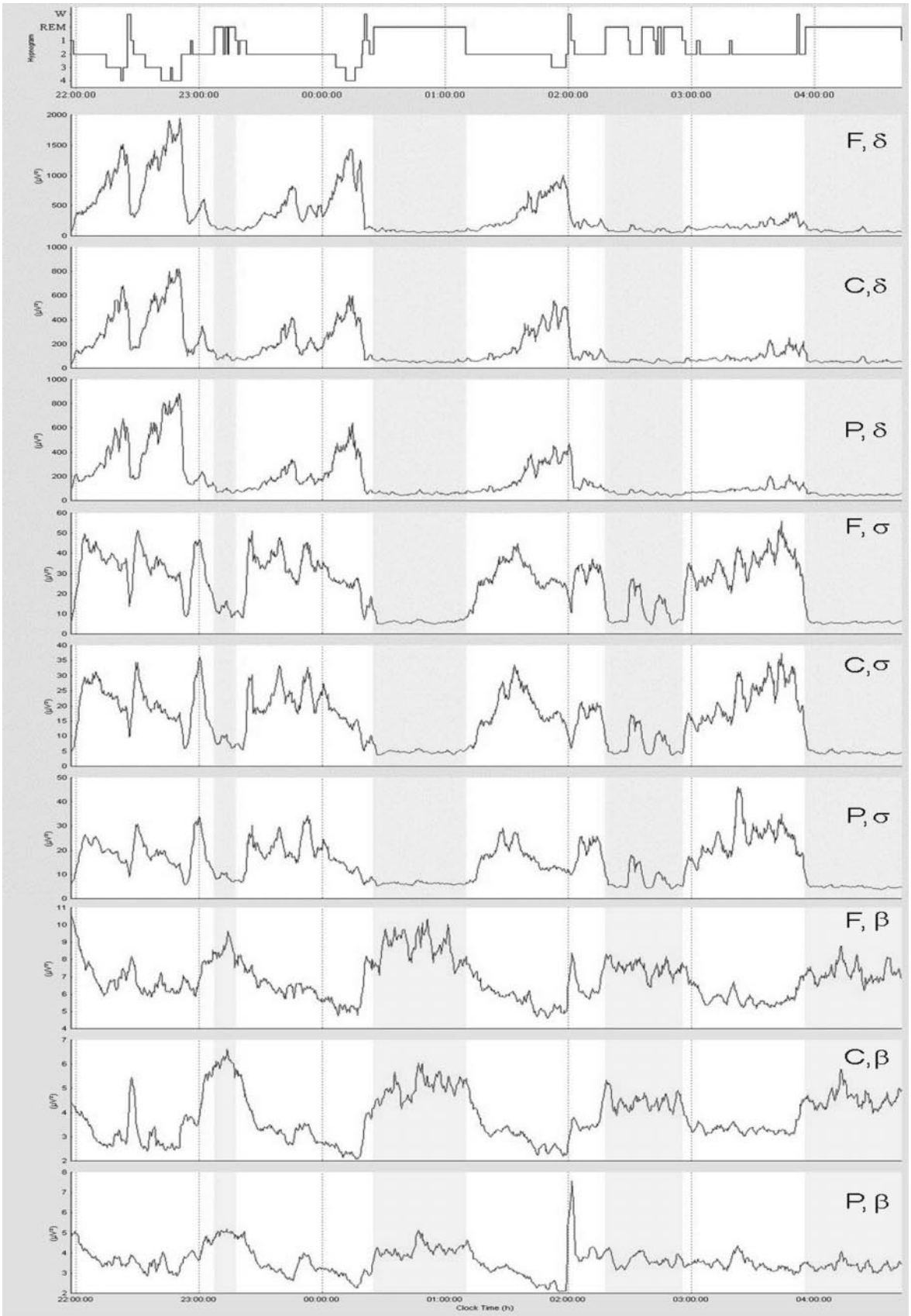

Figure 2. Power time-courses for a typical subject, across four NREM–REM sleep cycles for the delta (δ), sigma (σ) and beta (β) frequency bands measured at frontal (F), central (C) and parietal (P) sites, together with the corresponding hypnogram in the uppermost panel. W = wake; REM = REM sleep (grey-shaded); 1, 2, 3, 4 = NREM sleep stages. The total duration of the time-courses is 6 h 50 min with the hours indicated by vertical dashed lines.

Table 1
Cross-correlation coefficients between power time-courses in the different frequency bands measured at three different sites

		Delta (1–4 Hz)			Sigma (11–15 Hz)			Beta (15–35 Hz)		
		F	C	P	F	C	P	F	C	P
NREM 1	F	1.00			1.00			1.000		
	C	0.92	1.00		0.87	1.00		0.85	1.00	
	P	0.89	0.93	1.00	0.66	0.81	1.00	0.73	0.83	1.00
NREM 2	F	1.00			1.00			1.00		
	C	0.92	1.00		0.89	1.00		0.86	1.00	
	P	0.87	0.93	1.00	0.71	0.88	1.00	0.66	0.85	1.00
NREM 3	F	1.00			1.00			1.000		
	C	0.92	1.00		0.90	1.00		0.89	1.00	
	P	0.84	0.91	1.00	0.70	0.85	1.00	0.72	0.85	1.00
NREM 4	F	1.00			1.00			1.00		
	C	0.90	1.00		0.90	1.00		0.89	1.00	
	P	0.86	0.89	1.00	0.72	0.85	1.00	0.75	0.85	1.00

All correlation coefficients are statistically highly significant with associated Bonferroni probabilities <0.0001. F = Frontal with leads F4-Cz; C = central with leads C4-T4; P = parietal with leads Pz-O2.

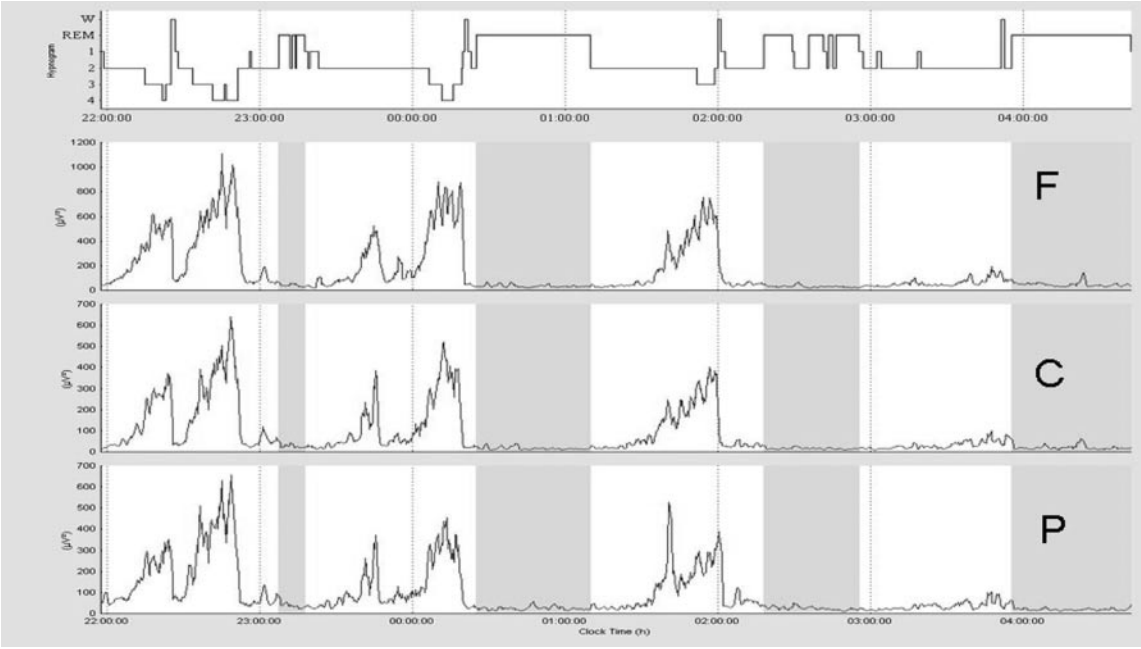

Figure 3. Power time-courses for the same subject as in Figure 2, across four NREM–REM sleep cycles for the cortically generated slow oscillation measured at frontal (F), central (C) and parietal (P) sites, together with the corresponding hypnogram in the uppermost panel. W = wake; REM = REM sleep (grey-shaded); 1, 2, 3, 4 = NREM sleep stages. The total duration of the time-courses is 6 h 50 min with the hours indicated by vertical dashed lines.

Table 2
Cross-correlation coefficients between cortically generated slow oscillation power time-courses measured at three different sites

	NREM 1			NREM 2			NREM 3			NREM 4		
	F	C	P	F	C	P	F	C	P	F	C	P
F	1.00			1.00			1.00			1.00		
C	0.90	1.00		0.90	1.00		0.89	1.00		0.84	1.00	
P	0.88	0.94	1.00	0.88	0.90	1.00	0.79	0.86	1.00	0.80	0.85	1.00

All correlation coefficients are statistically highly significant with associated Bonferroni probabilities <0.0001. F = Frontal with leads F4-Cz; C = central with leads C4-T4; P = parietal with leads Pz-O2.

types of brainstem-thalamic activating neurons. (iii) The detailed structure of the NREM episode presents repeated alternation towards and away from deep sleep (Merica and Fortune, 2000). Preliminary results (Merica and Prilipko, 2002) on a correlation between these alternations and the repeated occurrence within the episode of independently defined arousal events support the view that this behaviour is controlled via the arousal system.

It is of particular interest that the shape and timing of the

time-courses of the cortically generated slow oscillation, an essential component of the 'unified oscillatory machine', are almost identical at different sites, in the same manner as for the other bands. This we may have expected since the slow oscillation is modulated by the brainstem activating systems (Steriade *et al.*, 1993d). This result therefore supports the view that the slow oscillation power time-course across the NREM episode is determined at the brainstem. What, then, is the role of the cortex and the relationship of this role to the results of current studies on EEG time-courses? As already stated, the cortex has the essential task of generating the slow oscillation that triggers, shapes and synchronizes thalamically generated rhythms, which otherwise would not have sufficient amplitude to be effective at the EEG level. Animal data provide evidence on the major role of the cortex in ensuring the widespread synchronization and the quasi-simultaneous occurrence of spindles in thalamocortical systems. After removal of the cortex, although the spindles continue to occur with approximately the same temporal density at different thalamic locations (hence time–course curves remain unaltered), their coincidence on a 1 s timescale is disrupted. The observed simultaneity in spindle oscillation is determined by the corticothalamic neurons rather than by intracortical connectivity, since coronal section of the cortex does not disrupt this simultaneity (Contreras *et al.*, 1996). Thus the thalamus in collaboration with the cortex has the crucial role of translating the brainstem modulation of thalamocortical excitatory input into the production and amplification of the observed output sequences of spindles, slow waves and faster waves. In other words, the 'unified oscillatory machine' provides an amplification factor particular to each power time-course – without altering the basic shape and timing that is brainstem-determined. This amplification may be different for different sites, under the influence perhaps of use-dependent needs and anatomical considerations, leading to different levels for the average time-course power at these sites. This is observed in our data and reported by those above-cited authors who have focused on the issue of regional differences in average spectral power.

In conclusion, our results on the quasi-identical aspect of the time-courses at different sites on the cortex for each frequency band, together with current knowledge on brainstem modulatory control, lend considerable support to our hypothesis that the brainstem activating systems dictate the shape and timing of these time-courses. At the same time, the 'unified oscillatory machine' formed by the interaction between cortex and thalamus controls the generation and amplification of the waveforms making up the time-courses. This amplification of the time-courses by site-dependent scaling factors leads to regional differences in average power level as reported in the literature. In our view, the two phenomena are quite distinct: the first results in the ubiquitous propagation of a power intensity pattern emanating from the brainstem, and the second translates this pattern while generating and propagating the waveforms essential to sleep.

Notes

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Address correspondence to Helli Merica, Hôpitaux Universitaires de Genève, Laboratoire de Sommeil et de Neurophysiologie, 2 ch. Petit Bel-Air, 1225 Chêne-Bourg, Geneva, Switzerland. Email: helli.merica@hcuge.ch.

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